--35. A method for identifying compounds for modulating G-protein mediated signal transduction, comprising contacting a cell containing a receptor tyrosine kinase capable of activation by G-protein mediated signal transduction with a test compound suspected of being a modulator of a proteinase or a precursor of a ligand of the receptor tyrosine kinase, and evaluating G-protein mediated receptor tyrosine kinase activation upon exposure of the cell to said test compound.--

REMARKS

In the Office Action dated May 21, 2002, claims 1, 3-5 and 8-21, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks.

Claim 17 was objected to due to an informality. Claim 17 has been canceled rendering this objection moot.

Claims 1, 17-19 and 21 were rejected under 35 USC §112, first paragraph, as lacking enablement. Claims 1, 17-19 and 21 have been canceled and new claims added to the application. In view of the cancellation of claims 1, 17-19 and 21, this rejection is now moot.

Claims 1, 3-5 and 8-21 were rejected under 35 USC §112, second paragraph, as indefinite. Claims 1, 3-5 and 8-21 have been canceled and new claims added to the application. The new claims clarify the language found indefinite. In view of the cancellation of claims 1, 3-5 and 8-21 and the addition of new claims to the application, applicants contend that this rejection is moot.

Claims 1, 4, 5, 8-10, 12, 13, 15 and 20 were rejected under 35 USC §102(a) as anticipated by or alternatively as obvious over Dong. Claims 1, 4, 5, 8-10, 12, 13, 15 and 20 have been canceled and new claims added to the application that more clearly describe the present invention. Applicants respectfully point out that Dong describes a method for inhibiting EGFR overexpression and does not suggest the modulation of G-protein or G-protein coupled receptor associated disorders. Dong indicates that the broad spectrum metalloprotease inhibitor Batimastat reduces proliferation of EGFR dependent cell lines. This reduction does not provide any insights into how the EGFR ligand ectodomain shedding is initiated. In contrast, the present inventors have identified G-protein coupled receptors and their ligands as inducers of EGFR ligand ectodomain shedding. This includes and describes the process upstream of the metalloprotease activity. In other words, the present invention provides for an important link or cross-talk between the GPCR and receptor tyrosine kinase signaling systems via ligand ectodomain shedding which is not disclosed or suggested by Dong.

The key question discussed by Dong is how the autocrine signaling through the EGFR is mediated. Autocrine signaling means the mechanism by which the EGFR continuously stimulates the synthesis or production of proteins that in turn cause activation of EGFR. This feedback loop provides for continuous cell growth and ultimately disease progression. Dong's findings suggest that the proteins whose production is stimulated by EGFR are EGF-like ligand precursors and metalloproteases. In contrast to Dong, the present inventors have identified GPCR ligands as mediators of autocrine signaling through the EGFR. In other words, instead of upregulating EGF-like ligands and metalloproteases, the EGFR actually increases the production of GPCR

ligands, while the amount of the proteins described by Dong is not affected. The newly synthesized GPCR ligands are secreted from the cells as peptide hormones and subsequently trigger activation of the EGFR by binding to their cognate seven-transmembrane receptors. In view of the fact that Dong does not suggest or disclose a method for modulating G-protein mediated signal transduction, applicants request that this rejection be withdrawn.

Claim 11 was rejected under 35 USC §103(a) as unpatentable over Dong further in view of Miyoshi. The presently claimed invention is not obvious over Dong as discussed above. Miyoshi does not cure this deficiency as Miyoshi is cited only for the disclosure of a cell line which can produce pro-HB-EGF and does not disclose a method for modulating G-protein mediated signal transduction. In addition, if one skilled in the art were to combine Dong and Miyoshi, they would have predicted that the ectodomain of the proHB-EGF would be proteolytically released and subsequently bind to and activate the EGFR, which would result in the stimulation of cell growth. Surprisingly, Miyoshi observed the opposite effect, proHB-EGF suppressed cellular stimulation. Miyoshi's results would lead one to the conclusion that the proteolytic cleavage of proHB-EGF as suggested by Dong, does not occur. Applicants contend that one skilled in the art would not combine Dong and Miyoshi in view of the contrary results in these references. In view of the above discussion, applicants request that this rejection be withdrawn.

Applicants respectfully submit that all of claims 22-35 are in condition for allowance. If it is believed that the application is not in condition for allowance, it is

respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 01-2300.

Respectfully submitted,

for

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